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CONTRACTING ORGANIZATION:	The University of Texas Health Science Center at Houston
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14. ABSTRACT
The objective of this proposed study is to systematically define the clinical and logistical issues surrounding traditional open vascular surgery and catheter-based hemorrhage control. The hypothesis is that minimally invasive, device-driven and expert-led NCTH control techniques improve survival compared to traditional open vascular surgery. This project will achieve the following aims: 1) Determine current practice patterns for the treatment of patients with NCTH among 4 clinical sites using a retrospective study design (Phase 1a); 2) Conduct a 2-day Delphi Panel meeting of military and civilian experts to gain consensus regarding anatomic, technology, credentialing, competency, and training issues for catheter-based hemorrhage control (Phase 1b); 3) Conduct a prospective 4-site observational study to test the hypothesis that less-invasive device-driven and expert-led hemorrhage control techniques are associated with improved survival in NCTH patients and strengthen the evidence base to inform future development of catheters, devices, and training required for surgeons for catheter-based hemorrhage control (Phase 2). At the end of Y3, the retrospective study has been completed, the Delphi Meeting has been held and a manuscript describing the results has been drafted. In addition, the prospective study continues in all 4 sites, 228 patients have been enrolled, and we are awaiting an EWOF to extend the prospective study into year 4 for both enrollment and analysis.

15. SUBJECT TERMS
Trauma, vascular, hemorrhage, Non-compressible Torso Hemorrhage, coagulation, mortality

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INTRODUCTION

On September 15, 2014, the U.S. Army Medical Research Acquisition Activity (USAMRAA) awarded a 2-year contract to the University of Texas Health Science Center at Houston (UTHealth). This 2-phase project will systematically define the clinical and logistical issues surrounding traditional open vascular surgery and catheter-based hemorrhage control for non-compressible torso hemorrhage (NCTH). The hypothesis is that minimally invasive, device-driven and expert-led NCTH control techniques improve survival compared to traditional open vascular surgery. In addition to UTHealth, Baylor College of Medicine, the University of Texas Health Science Center at San Antonio (UTHSCSA) and the San Antonio Military Medical Center (SAMMC)/US Army Institute of Surgical Research (USAISR) are collaborating.

KEYWORDS
Trauma, Vascular, Hemorrhage, Non-compressible Torso Hemorrhage, Coagulation, Mortality

ACCOMPLISHMENTS
What were the major goals of the project?

Goals/Milestones – Phase I
1. Obtain DOD HPRO and local institutional review board (IRB) Approvals
2. Conduct retrospective data collection
3. Analysis of retrospective data
4. Hold Delphi Meeting

Goals/Milestones – Phase II
5. Obtain regulatory amendment approvals for prospective study
6. Conduct prospective observational study
7. Data Analysis/Publications

What was accomplished under these goals?
Milestone 1: Obtain USAMRMC HRPO and participating sites' IRB approvals
Y1Q1 UT Houston IRB approval for the retrospective study was received 18-NOV-2014. We submitted the USAMRMC Human Research Protections Office (HRPO) application on 02-DEC-2014 for review and approval. We also sent the UTHealth IRB approval and study documents to participating sites to submit to their local IRB review and approval. Baylor College of Medicine (BCM) and the University of Texas Health Science Center at San Antonio (UTHSCSA) submitted their local IRB applications in Q1.

Y1Q2 USAMRMC HRPO approval for the retrospective study at the UTHealth site was obtained 23-JAN-2015. UTHSCSA obtained their local IRB approval on 12-MAR-2015. BCM also received local IRB approval on 10-APR-2015. San Antonio Military Medical Center (SAMMC) requested that their site be changed to the US Army Institute of Surgical Research (USAISR) because USAISR had more developed human subjects and contracting processes. USAISR submitted documents to their IRB in Q2.

Y1Q3 UTHSCSA received HRPO approval for the retrospective study on 27-MAR-2015 and BCM received HRPO approval on 20-APR-2015.

Y1Q4 USAISR received local IRB and HRPO approval on 22-JUN-2015. UTHealth received local IRB approval for their continuing review on 31-AUG-2015.

Y2Q1 UTHealth received HRPO continuing review acknowledgement for the retrospective study on 09-OCT-2015.

Y2Q2 BCM and UTHSCSA received continuing review approval for the retrospective study from their local IRBs on 19-JAN-2016 and 17-FEB-2016, respectively.

Y2Q3 UTHealth received approval for the retrospective study continuing review on 23-MAY-2016. UTHSCSA and BCM continuing review acknowledgments for the retrospective study were also received from HRPO on 04-APR-2016 and 22-MAR-2016, respectively. USAISR received IRB and HRPO approval and acknowledgement of continuing review on 18-JUN-2016.

Y2Q4 UTHealth received acknowledgement of continuing review for the retrospective study on 17-AUG-2016.

Y3Q1 BCM received continuing review approval for the retrospective study on 20-OCT-2016.

Y3Q2 UTHealth and USHSCSA received continuing review approval for the retrospective study on 17-FEB-2017 and 14-FEB-2017, respectively. HRPO continuing review acknowledgement for the BCM retrospective study was received 07-MAR-2017.

Y3Q3 UTHealth requested continuing review acknowledgement from HRPO for the retrospective study on 09-MAR-2017. HRPO continuing review acknowledgement for the UTHSCSA retrospective study was received 23-MAY-2017.

Y3Q4 USAISR received continuing review approval for the retrospective study on 20-June-2017. All IRB and HRPO documents for the retrospective study can be found in Appendix 1.

Milestone 2: Initiate retrospective data collection study.
Y1Q1 Before the UTHealth IRB submission, we had a series of internal meetings as well as phone calls and emails with external investigators to discuss, revise, and finalize the protocol and case report forms for the retrospective study. The protocol and case report forms were finalized as of 15-NOV-2014. We also submitted information and study documents to UTHealth's Sponsored Projects Administration in order to begin drafting of the subcontracts for the three external sites as the next step to initiating data collection.

Y1Q2 The subcontracts with the three sites were drafted by UTHealth's Sponsored Projects Administration and sent to the three external sites as the first step to initiating data collection. The subcontracts were sent to the sites on 07-JAN-2015. Contract negotiation has taken longer than expected and at the end of Y1Q2, all three subcontracts were not yet executed. USAISR has requested a Cooperative Research and Development Agreement (CRADA) and a Data Use Agreement (DUA) for this study instead of the standard Federal Demonstration Partnership (FDP) contract we use for all other sites and projects. We expect that the contracts for BCM and UTHSCSA will be executed in early Q3. Because we have not received approval from the GOR for the change in PI for USAISR, we cannot move forward with the CRADA; however, the DUA can move forward. We have developed a REDCap application for the Phase 1 retrospective study, including a data dictionary, codebook and data entry forms. We are finalizing this database application. Once completed, UTHealth will start entering data into the application.

Y1Q3 UTHealth, UTHSCSA and BCM have begun the trauma registry query and retrospective data review. We received approval from the GOR for the change in PI and research site to USAISR. Contract negotiations continue with USAISR because they are using a Cooperative Research and Development Agreement (CRADA) instead of the standard Federal Demonstration Partnership (FDP) contract we developed for all sites. The Data Use Agreement (DUA) that ISR also required has been executed by both parties. The Program Manager at USISR contacted UTHealth on 25-June-2015 to request additional documents be sent to the Contract Officer at USAMRAA in order for the change in site to take effect. UTHealth sent the documents to her on

29-JUNE-2015. The REDCap application has been finalized and data entry into the system has begun.

Y1Q4 UTHealth requested a status update from the Contract Office at USAMRAA on 13-July-2015, and a response was received on 22-JULY-2015 stating that a modification was being prepared to change the study site. We received a request for additional documents on 08-OCT-2015 from USAMRAA.

Y2Q1 UTHealth, UTHSCSA and BCM completed trauma registry query and retrospective data review and data entry in Y2Q1. 239 patients from UTHealth, 189 from BCM, and 208 from UTHSCSA were enrolled. The Cooperative Research and Development Agreement (CRADA) between UTHealth and USAISR was also fully executed in Y2Q1. USAISR entered registry information on all of their eligible patients (N=51) and are continuing to enter additional detailed data from the medical record abstraction.

Y2Q2 USAISR completed retrospective study data entry in Y2Q2. A total of 683 for the four sites were therefore available for analysis. This number was considerably less than the expected total for enrollment (n=3500) due to the operationalization of the eligibility criteria. The eligibility criteria from both the proposal and the IRB-approved protocol were:

Inclusion Criteria

To be eligible, subjects must meet all of the following:

1) Has NCTH defined as
    a. Named axial torso vessel disruption
    b. Solid organ injury with AIS $\geq$ 4 (liver, kidney, or spleen) plus concomitant shock or immediate operation
    c. Thoracic cavity injury (including lung)
    d. Pelvic fracture with ring disruption
2) Estimated age of 15 years or older or greater than/equal to weight of 50 kg if age unknown
3) Admitted to one of four participating Level 1 trauma centers

Exclusion Criteria

Subjects will be excluded of they meet one or more of the following:

1) Patients who are <15 years old or under 50 kg body weight if age unknown
2) Known pregnancy reported by EMS personnel
3) Isolated hip fractures
4) Injury resulting from a fall from standing

For the original submitted grant proposal, we received data from all 4 sites in order to estimate the potential number of patients we would be able to enroll in the retrospective using these inclusion and exclusion criteria. Using these criteria only, we estimated that we would enroll 3500 patients. However, in order to operationalize these criteria for the retrospective study using site trauma registries to identify appropriate patients and to get detailed information regarding the specific vessels of interest, the following rules were used at all 4 sites:

a. Run the following inclusions/exclusions first:
    i. Inclusions:

1. Age 15 or older
2. Admitted
3. Time of injury < 12 hours from admission
    a. Not all of our patients have a time of injury in the registry, so we also used the date/time of EMS notification to try to catch any of those patients

ii. Exclusions:
1. Prisoners
2. Isolated hip fractures
3. Injury resulting from a fall from standing (< 6 feet)
4. Prisoners, defined as those who have been directly admitted from a correctional facility

b. Use that data set to separately find the patients with abdominal, thoracic, and pelvic injuries
i. Abdominal
1. We searched for patients with AIS >= 3 plus base deficit > 4
2. We searched for patients with AIS >= 3 plus immediate operation (limited it to patients that went directly from the ER to the OR within 90 minutes of arrival)
3. We then combined those two lists

ii. Thoracic
1. We searched for patients with AIS >= 3 plus base deficit > 4
2. We searched for patients with AIS >= 3 plus immediate operation (limited it to patients that went directly from the ER to the OR within 90 minutes of arrival)
3. We then combined those two lists

iii. Pelvic
1. We searched for patients with AIS05 codes equal to: 856161.3, 856162.4, 856163.4, 856164.5, 856171.4, 856172.4, 856173.5, or 856174.5

iv. Combine the above 3 lists (abdominal, thoracic, and pelvic)

c. Use that data set to separately find the patients with named axial torso vessel disruption using both AIS codes and ICD9 codes (to try to find as many as possible)
i. AIS codes
1. Thoracic arteries: 420206.4, 420208.4, 420210.5, 420216.5, 420218.6, 420404.3, 420406.3, 420408.4, 421004.3, 421006.3, 421008.5, 421009.6, 421404.3, 421406.3, 421408.4, 422004.2, 422006.2, 422008.3
2. Thoracic veins: 420602.3, 420604.3, 420606.4, 420608.5, 421202.3, 421204.3, 421206.5, 421207.6, 421602.3, 421604.3, 421606.4, 421802.3, 421804.3, 421806.4, 421808.5, 422202.2, 422204.2, 422206.3
3. Abdominal arteries: 520204.4, 520206.4, 520208.5, 520404.3, 520406.4, 520408.5, 520604.3, 520606.3, 520608.4, 521104.3, 521106.3, 521108.4, 521404.3, 521406.3, 521408.4, 541828.5

4. Abdominal veins: 520802.3, 520804.3, 520806.4, 521002.2, 521004.2, 521006.3, 521202.3, 521204.3, 521206.4, 521602.3, 521604.3, 521606.4
5. Common carotid arteries: 320206.3, 320208.3, 320209.3, 320210.4, 320211.4, 320212.4, 320213.4, 320214.5, 320215.5, 320216.3, 320217.3, 320218.4, 320219.4

ii. ICD9 codes
1. Thorax: 901.0, 901.1, 901.2, 901.3, 901.41, 901.42
2. Abdomen: 902.0, 902.10, 902.20, 902.22, 902.23, 902.25, 902.31, 902.33, 902.41, 902.42, 902.53, 902.54
3. Common carotid: 900.01

iii. Combine the AIS and ICD9 lists and produced our final patient list.

Using these rules to generate the sampling frame for patients, further exclusions were made if no specifically-named vessels were reported in the medical record. In the prospective study, we will be able to include solid organ injuries as well as vessel injuries.

Y2Q3 We initiated a study of CT data for vascular injuries in order to begin collecting data for questions we had originally planned to address in the prospective study. This substudy uses data only from UTHealth, where we have adequate image storage capabilities, and is approved under the retrospective study UTHealth IRB and HRPO approvals. The plan for this substudy is to accurately quantify the applicable vascular morphometry of the human torso, which can be done with images previously stored during the retrospective study. For the scan-based measurements, standard imaging software is used to measure diameter and length of the torso vessels and relative distances between major aortic branch vessels as related to aortic zones defined by Stannard, et al. We are also including a CT measurement component in the prospective study at UTHealth to continue this work.

Y2Q4 Data collection, entry and cleaning for the substudy of CT images for vascular injuries was largely completed in Y2Q4. One more field for 100 patients remains to be entered and will be completed in Y3Q1. We also negotiated Data Use Agreements (DUAs) with Madigan Army Medical Center (PI: COL Matthew Martin) and with Denver Health Medical Center (PI: Charles Fox) for their use of the retrospective study data. Both were executed early in Y3Q1.

Y3Q1 The retrospective study was completed as described in the SOW in Y2Q2. Data for the additional CT measurement substudy was completed in this quarter for a training set of data to predict catheter insertion length using external measurements and patient data such as sex, height, weight and body mass index (BMI). We performed a preliminary analysis of the data and identified likely algorithms to predict appropriate insertion to Zones I and III. The developed algorithm will be tested on data from an additional 100 patients that are now being collected. We also executed a Data Use Agreements (DUA) with Madigan Army Medical Center (PI: COL Matthew Martin) for use of the retrospective study data on 26-SEP-2016.

Y3Q2 We performed a preliminary analysis of the CT measurement substudy data and identified likely algorithms to predict appropriate insertion to Zones I and III. We continued to collect data

from an additional 100 patients in order to validate the algorithm and expected to complete this additional data collection in early Y3Q3.

Y3Q3 We completed data collection from the additional 100 patients in Y3Q3 and are currently validating the algorithm for the final development of the nonogram which we plan to copyright.

Y3Q4 We have completed data analysis for the CT measurement substudy and the manuscript is currently under development.

Milestone 3: Analysis of retrospective data

Y2Q1 We identified a Co-Investigator Statistician, Stacia DeSantis, PhD, who worked on preliminary statistical analysis code and programs. She obtained access to the dataset, the data dictionary, the protocol, and updated the statistical plan with assistance from a statistical programmer (T. Jay Greene, MS).

Y2Q2 Data analysis for the Delphi Meeting was completed during this quarter. Additional analysis was undertaken during this quarter as a result of suggestions made at the Delphi Meeting. These analyses will be reported in an upcoming manuscript. Additionally, all attendees of the Delphi Meeting were offered the opportunity to analyze the retrospective data. We are currently working with these external institutions and negotiating Data Use Agreements (DUAs) with them. Our goal is that additional manuscripts and/or abstracts will be submitted as a result of sharing these important data.

Y2Q3 The additional analyses initiated last quarter are ongoing. These analyses will be reported in an upcoming manuscript. Two external institutions (Madigan Army Medical Center and Denver Health Medical Center) requested the retrospective data for their own analysis. The UTHealth Sponsored Projects office completed the draft of the Data Use Agreement, which was sent to the two institutions for negotiation and execution in June 2016.

Y2Q4 We submitted an abstract of the retrospective study to the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting and it was accepted for an oral presentation at the meeting in January. We also drafted a manuscript for the main results of the retrospective study during Y2Q4 and it will be finalized in Y3Q1. Negotiation of the two DUAs continued this quarter.

Y3Q1 The main results manuscript for the retrospective study was finalized and submitted for review during this quarter.

Y3Q2 The main results manuscript for the retrospective study was presented at EAST and is under review at the J*ournal of Trauma and Acute Care Surgery*. COL Matthew Martin of Madigan Army Medical Center continued to work on a secondary analysis that hypothesizes that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients. The DUA with Denver Health Medical Center (PI: Charles Fox) was partially executed by UTHealth and awaiting full execution by Denver.

Y3Q3 The main results manuscript for the retrospective study was accepted at the J*ournal of Trauma and Acute Care Surgery* on 1-APR-2017. COL Matthew Martin of Madigan Army Medical Center continued to work on a secondary analysis that hypothesizes that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients. The DUA with Denver Health Medical Center (PI: Charles Fox) was fully executed.

Y3Q4 Retrospective data were sent to Denver Health Medical Center on 30-JUN-2017.The main results manuscript for the retrospective study was published in the July edition of the J*ournal of Trauma and Acute Care Surgery*. COL Matthew Martin of Madigan Army Medical Center submitted his secondary analysis that hypothesizing that the FAST exam has a high false negative rate when used in the evaluation of NCTH patients to EAST on 1-JUL-2017. Copies of the published manuscript and submitted abstract can be found in Appendix 2.

Milestone 4: Hold Delphi Meeting

Y2Q1 We updated the list of 20 potential Delphi Panel meeting attendees and received input on additional potential attendees from Col. Todd Rasmussen, an expert in non-compressible torso hemorrhage

Y2Q2 The Delphi Panel Meeting was held on March 7, 2016 at the University of Texas Health Science Center at Houston. A total of 27 people attended the meeting. Attendees included the site investigators and coordinators, trauma and vascular surgeons from civilian and military institutions, and the Houston Data Coordinating Center. The group reviewed the results of the retrospective study and provided input for the upcoming Phase II prospective, observational study. See the Y2Q2 report for the agenda and review of retrospective data used at the Delphi Meeting, notes from the meeting, and a list and picture of participants.

Y2Q3 Milestone complete, nothing to report

Y2Q4 Milestone complete, nothing to report

Y3Q1 Milestone complete, nothing to report

Y3Q2 Milestone complete, nothing to report

Y3Q3 Milestone complete, nothing to report

Y3Q4 Milestone complete, nothing to report

Milestone 5: Obtain regulatory amendment approvals for prospective study

Y2Q2 We refined a draft of the prospective study protocol based on recommendations and comments at the Delphi Meeting.

Y2Q3 We finalized the Phase II prospective protocol with the other site PIs and staff. The protocol was submitted to the UTHealth IRB on 27-MAY-2016.

Y2Q4 UTHealth received IRB approval on 20-JUL-2016. BCM submitted the protocol to their IRB during Y2Q4. Approval for BCM was received 21-SEP-2016. UTHSCSA applied for IRB reciprocity during this quarter and received approval from the UTHealth IRB on 12-SEP-2016. UTHealth and UTHSCSA submitted their approval documents to HRPO for review. USAISR prepared their documents for submission to the MRMC IRB/HRPO.

Y3Q1 UTHealth and UTHSCSA received HRPO approval for the prospective study on 05-OCT-2016. UTHSCSA used reciprocity and therefore received approval from UTHealth's IRB. BCM received Harris Health System approval on 21-SEPT-2016 (local BCM approval occurred on 17-AUG-2016), and HRPO approval was received on 17-OCT-2016 for the prospective study.

Y3Q2 UTHealth submitted a continuing review application to their local IRB this quarter. USAISR submitted to HRPO for initial review and approval at their site for the prospective study on 17-MAR-2017.

Y3Q3 UTHealth and UTHSCSA received continuing review approval from UTHealth's local IRB this quarter on 27-MAR-2017 and received HRPO acknowledgment on 12-JUN-2017. UTHealth also changed the PI from Dr. Holcomb to Dr. Moore and received approval for the change from the local IRB on 22-MAY-2017. The PI change was acknowledged by HRPO in the 12-JUN-2017 document.

Y3Q4 USAISR received initial local IRB and HRPO approval for the prospective study on 29-JUN-2017. Copies of all Y3Q4 regulatory documents can be found in Appendix 3.

<u>Milestone 6: Conduct prospective observational study</u>
Y2Q4 We drafted modifications of subawards for BCM and UTHSCSA to extend the date of contract and add the Phase II funds. Both contracts have been executed (BCM on 29-SEP-2016 and UTHSCSA on 30-SEP-2016). We are negotiating a CRADA modification with USAISR for the change in PI from LTC Kevin Chung to LTC Jennifer Gurney. It was signed by UTHealth on 20-SEPT-2016 and we are awaiting signature and full execution by USAISR. In preparation of study initiation, we developed a draft of the Manual of Operations and have circulated it to the 3 external sites for review and comment. We expect to enroll patients in Y3Q1.

Y3Q1 Modifications of subawards for BCM and UTHSCSA to extend the date of contract and add the Phase II funds were executed this quarter (BCM on 29-SEP-2016 and UTHSCSA on 30-SEP-2016). A CRADA modification with USAISR for the change in PI from LTC Kevin Chung to LTC Jennifer Gurney was executed on 27-JUL-2016. A second modification of the CRADA was initiated by USAISR during this quarter. The partially executed CRADA was returned to USAISR on 27-OCT-2016.

Training occurred at UTHealth, UTHSCSA and BCM during Y3Q1. Patient enrollment began at UTHealth on 07-NOV-2016 and 18 patients were enrolled by the end of Y3Q1. UTHSCSA is currently screening patients (started 12-DEC-2016), but had no enrollments by the end of Y3Q1.

Y3Q2 The second modification of the CRADA with USAISR was fully executed on 28-OCT-2016. At UTHealth, 125 patients were screened and 56 patients were enrolled by the end of

Y3Q2. UTHSCSA screened 84 patients with 18 enrollments in total by the end of Y3Q2. BCM screened 17 patients and enrolled 7 by the end of Y3Q2.

Y3Q3 At UTHealth, 526 patients were screened and 108 patients were enrolled by the end of Y3Q3. UTHSCSA screened a total of 265 patients and 37 enrollments by the end of Y3Q3. BCM screened 40 patients in total with 15 patients enrolled by the end of Y3Q3. One hundred sixty patients were enrolled by the end of Y3Q3.

Y3Q4 Total screened and enrollment by site at the end of Y3Q4 is shown below.

Site	**Screened**	**Enrolled**
UTHealth	1094	153
UTHSCSA	265	37
BCM	144	36
USAISR	127	2
Total	1630	228

Milestone 7: Data Analysis/Publications

Y2Q2 We worked on finalizing data analyses and developing a manuscript for the retrospective study.

Y2Q3 We continued to work on finalizing data analyses and developing a manuscript for the retrospective study.

Y2Q4 We submitted an abstract of the retrospective study to the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting on 01-JUL-2016 and it was accepted on 01-AUG-2016 for oral presentation at the meeting. We also drafted a manuscript for this presentation during Y2Q4.

Y3Q1 The main results manuscript for the retrospective study was finalized and submitted for review during this quarter.

Y3Q2 The main results manuscript for the retrospective study was presented at the Eastern Association for the Surgery of Trauma (EAST) Annual Meeting in January 2017. The manuscript was revised and resubmitted for publication in the *Journal of Trauma and Acute Care Surgery* this quarter

Y3Q3 The main results manuscript for the retrospective study was accepted by the *Journal of Trauma and Acute Care Surgery* this quarter. Charles Wade, PhD, attended the JPC-6/CCCRP FSERCC Portfolio In-Progress Review on 02-MAY-2017.

Y3Q4 The main results manuscript for the retrospective study was published in the July edition of the J*ournal of Trauma and Acute Care Surgery* (Appendix 2). When data enrollment is complete for the prospective study, we will analyze the data and develop a main results manuscript.

What opportunities for training and professional development has the project provided?
Nothing to report.

How were the results disseminated to communities of interest?
Nothing to report. Results will be disseminated at the end of the project and as publications and presentations are accepted.

What do you plan to do during the next reporting period to accomplish the goals?
Milestone 1: Obtain USAMRMC HRPO and participating sites' IRB approvals
During Y4 of the project, we will ensure that the sites continue to submit continuing review approvals for the retrospective study to their local IRBs and HRPO in order to continue data analysis and manuscript development. We will also ensure that any Delphi Meeting attendees who have signed DUAs in order to perform their own data analysis will maintain appropriate regulatory approvals.

Milestone 2: Initiate retrospective data collection study
Milestone complete.

Milestone 3: Analysis of retrospective data
Analysis of the retrospective data will continue for development of additional secondary manuscripts, especially by COL Matthew Martin and Dr. Charles Fox. The manuscript for the CT measurement substudy will be finalized in Y4.

Milestone 4: Hold Delphi Meeting
Milestone complete.

Milestone 5: Obtain regulatory amendment approvals for prospective study
During Y4 of the project, we will ensure that the sites submit continuing reviews for the prospective study to their local IRBs and HRPO in order to complete the study.

Milestone 6: Conduct prospective observational study
We will continue enrolling patients in the prospective study until February 1 under the second EWOF. After February 1, data cleaning and analysis will occur as well as development of a main results manuscript.

Milestone 7: Data Analysis/Publications
After enrollment is complete on February 1, data cleaning and analysis will occur as well as development of a main results manuscript. The manuscript will be finalized by the end of the second EWOF.

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfers?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

We are approximately 1.5 years behind due to various issues from early in the project that have since been solved and delays in getting regulatory approvals at all four sites for the prospective study. We are awaiting a second one-year extension without funds, and we will continue to enroll patients for 4.5 additional months (until 01-FEB-2018), then clean the data, perform the analysis and develop manuscripts.

Changes that had a significant impact on expenditures

Because of a later start than anticipated, sites spent their Phase I funding more slowly than expected and any remaining funds were rolled into Phase II. At UTHealth, we also decreased paid effort on the project between July and September 2016 while awaiting regulatory approvals in order to save any remaining funding for the prospective study. USAISR has not submitted any invoices for the prospective study to date and thus have their full amount of Phase II funding at this time.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

PRODUCTS
Publications, conference papers, and presentations

Manuscripts

Chang R, Fox EE, Greene TJ, Eastridge BJ, Gilani R, Chung KK, DeSantis SM, DuBose JJ, Tomasek TS, Fortuna GR, Sames VG, Todd SR, Podbielski JM, Wade CE, Holcomb JB and the NTCH Study Group. Multicenter retrospective study of non-compressible torso hemorrhage: anatomic locations of bleeding and comparison of endovascular versus open approach. *J Trauma Acute Care Surg*. 2017;83(1):11-18. PMID: 28632581. PMCID: PMC5484539.

Presentations

Chang R, Fox EE, Greene TJ, Eastridge BJ, Gilani R, Chung KK, DeSantis SM, DuBose JJ, Tomasek JS, Fortuna GR, Sams VG, Todd SR, Podbielski JM, Wade CE, Holcomb JB. Multicenter retrospective study of non-compressible torso hemorrhage: anatomic locations of bleeding and comparison of endovascular versus open approach. Eastern Association for the Surgery of Trauma, Hollywood, FL, January 2017.

Website(s) or other Internet site(s)
Nothing to report.

Technologies or techniques
Nothing to report

Inventions, patent applications, and/or licenses
Nothing to report

Other Products
Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
What individuals have worked on the project?

Name:	John Holcomb, MD
Project Role:	Principal Investigator
Nearest Person Months Worked:	1
Contribution to Project:	Dr. Holcomb oversaw all aspects of study management and execution for both the retrospective and prospective studies until April 1, 2017, when he stepped down as PI for personal reasons. He oversaw all study staff, regulatory submissions, patient screening, subject enrollment, and data collection. He actively communicated with all clinical sites for this study, coordinated administration across institutions and ensured accurate and timely data collection and transfer.
Funding Source:	DOD W81XWH-14-1-0112

Name:	Laura J. Moore, MD
Project Role:	Principal Investigator
Nearest Person Months Worked:	1
Contribution to Project:	Dr. Moore oversaw all aspects of study management and execution for both the retrospective and prospective studies starting April 1, 2017. She oversaw all study staff, regulatory submissions, patient screening, subject enrollment, and data collection. She actively communicated with all clinical sites for this study, coordinated administration across institutions and ensured accurate and timely data collection and transfer.
Funding Source:	DOD W81XWH-14-1-0112

Name:	Erin Fox, PhD
Project Role:	Co-Investigator; Project Manager
Nearest Person Months Worked:	2
Contribution to Project:	Dr. Fox oversees the day-to-day communication and overall study coordination for both the retrospective and prospective multisite studies. She ensures timely and accurate reporting, including financial and interim research reports. She participated in the creation of the data management system and the Manual of Operation, data cleaning and integration, and coordination of requested data to research investigators in the retrospective study and will perform similar duties in the prospective study. She coordinated the subcontracts and budgets for the research sites. Dr. Fox is also involved with the analysis of data, interpretation of results, and development of manuscripts for this project.

Funding Source: DOD W81XWH-14-1-0112

Name: Charles Wade, PhD
Project Role: Co-Investigator
Nearest Person Months Worked: 1
Contribution to Project: Dr. Wade participated in the creation of the data management system and the Manual of Operation, data cleaning and integration, and coordination of requested data to research investigators.
Funding Source: DOD W81XWH-14-1-0112

Name: Jeanette Podbielski, RN
Project Role: Clinical Program/Regulatory Director
Nearest Person Months Worked: 1
Contribution to Project: Ms. Podbielski managed all regulatory aspects of this study. She assisted with study coordination as well as IRB preparation and submission. She managed the activities of the Research Coordinator and Assistant. Ms. Podbielski is the main point of contact for the external sites for regulatory issues, patient enrollment, and data collection.
Funding Source: DOD W81XWH-14-1-0112

Name: Denis Hinds, RN
Project Role: Research Coordinator
Nearest Person Months Worked: 3
Contribution to Project: Ms. Hinds assisted with all aspects of study coordination, including the attainment and maintenance of all necessary regulatory approvals and guidelines as well as patient enrollment, data collection, data entry, and answering queries at the UTHealth site for the prospective study.
Funding Source: DOD W81XWH-14-1-0112

Name: Amanda Haymaker
Project Role: Research Coordinator
Nearest Person Months Worked: 1
Contribution to Project: Ms. Haymaker assisted with all aspects of study coordination, including the attainment and maintenance of all necessary regulatory approvals and guidelines as well as patient enrollment, data collection, data entry, and answering queries at the UTHealth site for the prospective study.
Funding Source: DOD W81XWH-14-1-0112

Name: Marc Dipasupil
Project Role: Research Assistant

Nearest Person Months Worked: 1
Contribution to Project: Mr. Dipasupil assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.
Funding Source: DOD W81XWH-14-1-0112

Name: Kandice Motley
Project Role: Research Assistant
Nearest Person Months Worked: 5
Contribution to Project: Ms. Motley assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.
Funding Source: DOD W81XWH-14-1-0112

Name: Christy Allen
Project Role: Research Assistant
Nearest Person Months Worked: 1
Contribution to Project: Ms. Allen assisted in identifying eligible patients, performing data collection, and entering data at the UTHealth site in the prospective study.
Funding Source: DOD W81XWH-14-1-0112

Name: Jeff Tomasek, MD
Project Role: Research Assistant
Nearest Person Months Worked: 2
Contribution to Project: Dr. Tomasek identified an appropriate population of patients through the trauma registry, set-up the REDCap database, provided training for the external sites, and coordinates the collection of data from the four clinical sites into the central database used for analysis of the prospective study.
Funding Source: DOD W81XWH-14-1-0112

Name: Stacia DeSantis, PhD
Project Role: Co-Investigator (Statistician)
Nearest Person Months Worked: 1
Contribution to Project: Dr. DeSantis is the lead statistician for this project. She oversees all data management and analysis for both the retrospective and prospective studies.
Funding Source: DOD W81XWH-14-1-0112

Name: T. Jay Greene, MS
Project Role: Graduate Research Assistant (Statistical Programmer)
Nearest Person Months Worked: 2

Contribution to Project:	Mr. Green acts as the statistical programmer for both the retrospective and prospective studies and is supervised by Dr. DeSantis.
Funding Source:	DOD W81XWH-14-1-0112

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

We requested a change in PI on 31-MAY-2017 from John Holcomb, MD, to Laura J. Moore, MD. Dr. Holcomb is no longer considered key personnel on this project. Dr. Moore's active other support is as follows:

Title:	FiO2 Closed Loop Control in the ZOLL 731 Series Ventilator
Time Commitment:	4%
Agency:	University of Cincinnati/ZOLL Medical/USAF/AFMC, Jay Johanningman, MD
Agency POC:	S. Theresa Yockey, University of Cincinnati, Sponsored Research Services, 51 Goodman Avenue, Suite 530, Cincinnati, OH 45221-0222; 513-556-4390
Performance Period:	05/2015-05/2018
Role:	Principal Investigator
Level of Funding:	$220,000
Goals:	To demonstrate that physiologic closed-loop control (PCLC) is at least as safe and effective as manual control in keeping hemoglobin oxygen saturation (SpO_2) within the target range of 92-96%.

Title:	The PROspective Observational Vascular Injury Trial (PROOVIT)
Time Commitment:	2%
Agency:	National Trauma Institute/DOD/Army Medical Research Acquisition Activity
Agency PoC:	Jennifer Shankle, Grants Specialist, Jennifer.e.shankle.civ@mail.mil
Performance Period:	12/2015-11/2017
Role:	Site Principal Investigator
Level of Funding:	$79,186
Goals:	The major goal of this project is to establish a prospective, multicenter, observational study through the AAST Multicenter Trials Committee.

Title:	Multicenter, Observational Clinical Study of the ER-REBOA Catheter
Time Commitment:	25%
Agency:	Prytime Medical Devices, Inc./USAMMA/W911QY-15-C-0099
Agency POC:	David Spencer, CEO, Prytime Medical Devices, Inc., 229 N. Main Street, Boerne, TX 78006; dspencer@prytimemedical.com
Performance Period:	04/2017-06/2018
Role:	Principal Investigator
Level of Funding:	$1,248,137
Goals:	The purpose of this multicenter, prospective, observational study is

	to collect detailed information at selected Level 1 trauma centers currently utilizing the Prytime REBOA catheter as part of their standard clinical practice.

Support for Charles Wade, PhD has also changed. This current active support is as follows:

Title:	Pragmatic Randomized Optimal Platelet and Plasma Ratio (PROPPR)
Time Commitment:	50% (Principal Investigator)
Supporting Agency:	National Heart, Lung, and Blood Institute (2)
Agency Contact:	Dr. Gail Pearson, pearsong@nhlbi.nih.gov 31 Center Drive RKL2 Rm.8104, Bethesda, MD 20892, 301-435-0510
Performance Period:	10/2010-09/2017
Annual Direct Costs:	$3,051,148
Project Goals:	To conduct a Phase III multi-site, randomized trial comparing the efficacy and safety of 1:1:1 transfusion ratios of plasma and platelets to red blood cells, with a 1:1:2 ratio in trauma patients.

Title:	Postdoctoral Training in Trauma and Hemorrhagic Shock
Time Commitment:	Primary Mentor/Considered Part of Academic Responsibilities
Supporting Agency:	NIH/NIGMS (T32GM008792)
Agency Contact:	Scott Somers, Ph.D., somerss@nigms.nih.gov 45 Center Dr. Rm 2As.49H, MSC 6200, Bethesda, MD 20892, 301-594-3827
Performance Period:	07/2012-06/2018
Annual Direct Costs:	$331,296
Project Goals:	The goal of the program is to prepare researchers to become academically competitive, translational scientists (both MD's and PhD's) who can design and execute laboratory models to test clinically-relevant hypotheses, collaborate with other scientists to enhance the basic understanding of the problem they are studying, initiate clinical trials, and clinically translate this information.

Title:	Combination therapies for the mitigation of musculoskeletal pathologic damage in a novel model of severe injury and disuse
Time Commitment:	5% (Principal Investigator)
Supporting Agency:	Department of Defense (CDMRP)
Agency Contact:	help@cdmrp.org 1077 Patchel St., Fort Detrick, MD 21702-5024, 301-682-5507
Performance Period:	09/2013-9/2017
Annual Direct Costs:	$157,800
Project Goals:	The goal of this project is to determine if the combination of exercise and the use of insulin or oxandrolone will synergistically improve muscle strength, bone health, and subsequent function to improve quality of life in burn patients.

Title:	Identification and Validation of Established and Novel Biomarkers

	for Infections in Burns
Time Commitment:	2% Co-Principal Investigators
Supporting Agency:	The University of Texas Medical Branch at Galveston/DOD USAMRAA (W81XWH-14-0162)
Agency Contact:	Celeste Finnerty, Ph.D./Doug Medcalf, douglas.a.medcal.civ@mail.mill, 301-619-2394
Performance Period:	09/2014-09/2018
Annual Direct Goals:	$48,851
Project Goals:	The measurement of already identified biomarkers alongside novel biomarkers identified with discovery proteomics can improve identification of risk for infection and identify the early stages of infection prior to clinical detection.

Title:	Prehospital Resuscitation on Helicopter Study (PROHS)
Time Commitment:	15%
Agency:	NIH/NHLBI
Agency PoC:	Gail Pearson, M.D., 301-435-0510, pearsong@mail.nih.gov
Performance Period:	1/2015-12/2017
Role:	Principal Investigator
Level of Funding:	$2,383,399
Goals:	The goal of this project is to perform a multicenter prospective observational study of air ambulance-based prehospital resuscitation regimens currently utilized at 9 participating sites.

Title:	Optimizing Outcomes for Soldiers with Burn Injury: Protective Effects of Propranolol in Adults Following Major Burn Injury
Time Commitment:	2%
Agency:	American Burn Association/DOD (W81XWH-11-1-0835)
Agency PoC:	Not Available
Performance Period:	2/2016-10/2017
Role:	Site Principal Investigator
Level of Funding:	$89,455
Goals:	To determine if the non-selective beta blockade agent propranolol can reduce cardiac rate pressure product without increasing risk of adverse event when compared to placebo.

Title:	aRandomized trial of ENtERal Glutamine to MinimIZE thermal injury
Time Commitment:	2%
Agency:	Queen's University at Kingston and KGHRI, Canadian Institutes of Health Research (CIHR)
Agency POC:	Not Available
Performance Period:	06/2016-12/2020
Role:	Site Co-Investigator
Level of Funding:	$84,919

Goals**:** The goal is to provide the rationale for a large, multicenter clinical trial of supplemental enteral glutamine in 2700 severe burn injury patients.

What other organizations were involved as partners?

Baylor College of Medicine
Houston, TX
Research collaborator

University of Texas Health Science Center at San Antonio
San Antonio, TX
Research collaborator

US Army Institute of Surgical Research
San Antonio, TX
Research collaborator

SPECIAL REPORTING REQUIREMENTS
Quad Chart uploaded as Appendix 4.

APPENDICES

Appendix 1. Regulatory documents for the retrospective study from Y3Q4

DEPARTMENT OF THE ARMY
HEADQUARTERS, US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
810 SCHREIDER STREET
FORT DETRICK, MD 21702-5000

REPLY TO
ATTENTION OF

MCMR-RPI 20 June 2017

MEMORANDUM FOR RECORD

SUBJECT: Continuing Review Approval for the Protocol, "Hemorrhage Control for Major Traumatic Vascular Injuries Phase I: A Retrospective Analysis of Non-Compressible Torso Hemorrhage (NCTH)," Principal Investigator: LTC Jennifer Gurney, MC, US Army Institute of Surgical Research (USAISR), Joint Base San Antonio, Fort Sam Houston, TX, in Support of the Proposal "Hemorrhage Control for Major Traumatic Vascular Injuries," Proposal Principal Investigator: John Holcomb, MD, University of Texas Health Science Center, Houston, Proposal Number 13057176, Award Number W81XWH-14-1-0112, HRPO Log Number A-18067, USAISR Protocol H-15-004, IRB Protocol Number M-10446

1. The Headquarters, US Army Medical Research and Materiel Command Institutional Review Board (HQ USAMRMC IRB) initially approved the above-referenced minimal risk research protocol via expedited review procedure on 21 June 2015 with waiver of informed consent and HIPAA authorization.

2. The HQ USAMRMC IRB received a continuation report on 25 May 2017. The study is open for data analysis only.

3. The protocol and continuation report were reviewed via an expedited review procedure in accordance with 32 CFR 219.110(b)(1). The protocol remains in compliance with Federal, DOD, and US Army human subjects protection requirements. The research protocol (Site-specific Protocol Version 3, dated 3 August 2016) is approved for a period of one year, expiring 20 June 2018. Note that the continuing review date is set based on the current expiration date of 20 June 2017.

4. Please note the following requirements:

a. Submit all proposed changes to the study for review and approval by the HQ USAMRMC IRB before initiating the changes.

b. Promptly report to the HQ USAMRMC IRB:

(1) All unanticipated problems involving risks to subjects or others and related serious adverse events.

MCMR-RPI
SUBJECT: Continuing Review Approval for the Protocol, "Hemorrhage Control for Major Traumatic Vascular Injuries Phase I: A Retrospective Analysis of Non-Compressible Torso Hemorrhage (NCTH)," Principal Investigator: LTC Kevin Chung, MC, US Army Institute of Surgical Research (USAISR), Joint Base San Antonio, Fort Sam Houston, TX, in Support of the Proposal "Hemorrhage Control for Major Traumatic Vascular Injuries," Proposal Principal Investigator: John Holcomb, MD, University of Texas Health Science Center, Houston, Proposal Number 13057176, Award Number W81XWH-14-1-0112, HRPO Log Number A-18067, USAISR Protocol H-15-004, IRB Protocol Number M-10446

(2) Any protocol deviation that affects subjects' safety or rights and/or the integrity of the study.

c. Submit a continuation report, a copy of the current protocol and supporting documents to the HQ USAMRMC IRB at least 30 days prior to IRB approval expiration to ensure timely review and approval.

d. Submit a final study report and request to close the protocol upon completion of all research activities.

5. The Office of Research Protections IRB Office point of contact for this action is Debra DePaul, RN, MSN, General Dynamics Health Solutions, at 301-619-2620 or debra.depaul.ctr@mail.mil.

DEVON O REED
LTC, MS
Designated Expedited Review IRB Member
Headquarters, U.S. Army Medical Research
and Materiel Command
Institutional Review Board

Appendix 2. Manuscripts and abstracts

Multicenter retrospective study of noncompressible torso hemorrhage: Anatomic locations of bleeding and comparison of endovascular versus open approach

Ronald Chang, MD, Erin E. Fox, PhD, Thomas J. Greene, MPH, Brian J. Eastridge, MD, Ramyar Gilani, MD, Kevin K. Chung, MD, Stacia M. DeSantis, PhD, Joseph J. DuBose, MD, Jeffrey S. Tomasek, MD, Gerald R. Fortuna, Jr., MD, Valerie G. Sams, MD, S. Rob Todd, MD, Jeanette M. Podbielski, RN, Charles E. Wade, PhD, John B. Holcomb, MD, *and* **the NCTH Study Group***, Houston, Texas*

BACKGROUND: Rational development of technology for rapid control of noncompressible torso hemorrhage (NCTH) requires detailed understanding of what is bleeding. Our objectives were to describe the anatomic location of truncal bleeding in patients presenting with NCTH and compare endovascular (ENDO) management versus open (OPEN) management.

METHODS: This is a retrospective study of adult trauma patients with NCTH admitted to four urban Level I trauma centers in the Houston and San Antonio metropolitan areas in 2008 to 2012. Inclusion criteria include named axial torso vessel disruption, Abbreviated Injury Scale chest or abdomen score of 3 or higher with shock (base excess, <−4) or truncal operation in 90 minutes or less, or pelvic fracture with ring disruption. Exclusion criteria include isolated hip fractures, falls from standing, or prehospital cardiopulmonary resuscitation. After dichotomizing into OPEN, ENDO, and resuscitative thoracotomy (RT) groups based on the initial approach to control NCTH, a mixed-effects Poisson regression with robust error variance (controlling for age, mechanism, Injury Severity Score, shock, hypotension, and severe head injury as fixed effects and site as a random effect) was used to test the hypothesis that ENDO was associated with reduced in-hospital mortality in NCTH patients.

RESULTS: Five hundred forty-three patients with NCTH underwent ENDO (n = 166, 31%), OPEN (n = 309, 57%), or RT (n = 68, 12%). Anatomic bleeding locations were 25% chest, 41% abdomen, and 31% pelvis. ENDO was used to treat relatively few types of vascular injuries, whereas OPEN and RT injuries were more diverse. ENDO patients had more blunt trauma (95% vs. 34% vs. 32%); severe injuries (median Injury Severity Score, 34 vs. 27 vs. 21), and increased time to intervention (median, 298 vs. 92 vs. 51 minutes) compared with OPEN and RT. Mortality was 15% versus 20% versus 79%. ENDO was associated with decreased mortality compared to OPEN (relative risk, 0.58; 95% confidence interval, 0.46–0.73).

CONCLUSION: Although ENDO may reduce mortality in NCTH patients, significant group differences limit the generalizability of this finding. (*J Trauma Acute Care Surg.* 2017;83: 11–18. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic, level V.

KEY WORDS: Noncompressible torso hemorrhage; angioembolization; endovascular hemorrhage control.

Hemorrhage is the leading cause of potentially preventable civilian[1,2] and military[3] trauma deaths. In contrast to other causes of trauma death, exsanguination occurs rapidly (median of 2–3 hours after presentation).[4–8] Although great progress has been made in the rapid control of compressible hemorrhage, especially the use of tourniquets for extremity hemorrhage,[9–11] initial management of noncompressible torso hemorrhage (NCTH) from thoracic, abdominal, and pelvic sources still presents a significant challenge.[11,12] A retrospective review of 4,596 combat casualty mortalities from 2001 to 2011 in Afghanistan and Iraq found that 24% of deaths were potentially preventable and related to delayed or lack of hemorrhage control. Of the potentially preventable deaths, 67% were due to NCTH.[11] An epidemiologic study of the National Trauma Data Bank found that patients admitted to civilian trauma centers with NCTH and hypotension had nearly 50% mortality.[12]

Until recently, expeditious open (OPEN) thoracotomy and/or laparotomy were required for patients in hemorrhagic shock. Endovascular (ENDO) interventions were reserved for patients who were stable enough to undergo diagnostic studies revealing the injured vessel. The advent of hybrid operating rooms, where OPEN and ENDO techniques can be used as needed, has made possible the more frequent use of minimally invasive approaches for definitive control of NCTH in severely and multiply-injured patients.[13] However, both precise anatomic descriptions of the

Submitted: December 1, 2016, Revised: April 7, 2017, Accepted: April 12, 2017, Published online: April 27, 2017.

From the Center for Translational Injury Research (R.C., E.E.F., J.S.T., J.M.P., C.E.W., J.B.H.), Department of Surgery (R.C., E.E.F., C.E.W., J.B.H.), McGovern Medical School; Department of Biostatistics (T.J.G., S.M.D.), School of Public Health, Department of Surgery (B.J.E.), University of Texas Health Science Center at San Antonio, San Antonio; Michael E. DeBakey Department of Surgery (R.G., S.R.T.), Baylor College of Medicine, Houston; United States Army Institute of Surgical Research (K.K.C.); San Antonio Military Medical Center (V.G.S.), Fort Sam Houston; and Department of Cardiothoracic and Vascular Surgery (J.J.D., G.R.F., McGovern Medical School, University of Texas Health Science Center at Houston, Houston, Texas).

This study was presented at the 30th EAST Annual Assembly on January 13, 2017.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for reprints: Ronald Chang, MD, 6410 Fannin St. Suite 1100, Houston, TX 77030; email: ronald.chang@uth.tmc.edu.

DOI: 10.1097/TA.0000000000001530

source(s) of NCTH and comparisons of ENDO versus OPEN techniques for hemorrhage control are lacking. The objective of this study was twofold: first, to describe the precise anatomic locations of bleeding in a population of adult trauma patients with NCTH, and second, to test the hypothesis that the ENDO versus OPEN approach was associated with reduced mortality in trauma patients presenting with NCTH.

PATIENTS AND METHODS

Study Design

Approval was obtained from the institutional review boards of all four study sites: the University of Texas Health Science Center at Houston (UTHealth), Baylor College of Medicine, the University of Texas Health Science Center at San Antonio, and the San Antonio Military Medical Center as well as the Human Research Protections Office of the US Army Medical Research and Materiel Command. The four study sites represent all of the adult Level I trauma centers for the Houston and San Antonio metropolitan areas; they collectively serve a population of 5.85 million,[14,15] or 2.5% of the US adult population.[16]

Each institutional trauma registry was queried to identify trauma patients who presented between 2008 and 2012 with NCTH defined as (1) named axial torso vessel disruption, (2) Abbreviated Injury Scale (AIS) chest or abdomen score of 3 or greater with concomitant shock (base excess, <−4) or emergent operation (≤90 minutes after presentation), or (3) pelvic fracture with ring disruption. Patients who had an isolated hip fracture or isolated fall from standing were excluded. Demographic information, admission vital signs and laboratory studies, AIS and Injury Severity Score (ISS), transfusion of blood products, intensive care unit (ICU)-free days, and mortality were obtained from the institutional trauma registry and/or medical record. Cause of death was obtained from the institutional trauma registry. Radiological and/or operative reports were reviewed to describe as specifically as possible the anatomic location of NCTH or the specific vessel injured. Patients were divided into three groups based on the initial approach to hemorrhage control: OPEN (without resuscitative thoracotomy [RT]), ENDO (including REBOA), and RT). RT patients were grouped separately due to the ramifications of this therapy. Patients who did not undergo one of these procedures or who had prehospital cardiopulmonary resuscitation were excluded. Patients with documented OPEN and ENDO procedures for initial control of one or more sources of NCTH were categorized as the more invasive modality (OPEN). Study data were collected and managed at UTHealth using Research Electronic Data Capture,[17] a secure, Web-based application designed to support data capture for research studies.

Statistical Analysis

Statistical analysis was performed using Stata 14.1 (StataCorp LP, College Station, TX). Data are reported as median values with interquartile range or proportions as appropriate. Categorical data were analyzed by the χ^2 test or Fisher's exact test for categories with five patients or less. Nonparametric comparisons of continuous variables were performed using the Kruskal-Wallis test. If significant, *post hoc* pairwise comparisons with Holm-Bonferroni adjustments were performed using the Wilcoxon rank-sum test for continuous data and χ^2 or Fisher's exact test for categorical data. To test the hypothesis that ENDO was associated with decreased in-hospital mortality compared with OPEN, we used a mixed-effects Poisson regression with robust error variance, which has been described as a method to estimate relative risks (RR) for a binary outcome.[18] We controlled for age, ISS, mechanism, severe head injury (AIS head ≥3), shock (base excess, ≤4 mEq/L), and hypotension (systolic blood pressure [SBP], <90 mm Hg) as fixed effects and site as a random effect. Subgroup analyses were performed based on the body cavity of hemorrhage (chest, abdomen, or pelvis). Missing base excess and SBP data were imputed with predictive mean matching (20 imputations) using age, ISS, AIS scores, mechanism, and treatment (ENDO vs. OPEN vs. RT). An alpha level of 0.05 was used for all statistical tests.

RESULTS

Demographics

During the 5-year study period, 678 patients with NCTH were included. A total of 135 patients were excluded (56 with prehospital cardiopulmonary resuscitation, 54 who did not undergo a procedure for hemorrhage control, 15 who died before an intervention was performed, and 10 with missing procedure data), leaving 543 (80%) patients who underwent ENDO (n = 166, 31%), OPEN (n = 309, 57%), or RT (n = 68, 12%). The number of included patients per site was 203, 171, 128, and 41, respectively. Use of ENDO significantly increased from 21% in 2008 to 41% in 2012 ($p < 0.01$). Only one patient in the ENDO group underwent REBOA. Nine (3%) OPEN patients also underwent an ENDO procedure for initial control of NCTH.

Demographics and admission parameters are summarized in Table 1. Patients in the ENDO group were older, had higher incidence of blunt mechanism, and had higher ISS, as well as much longer times to intervention than OPEN or RT patients.

Blood Product Transfusions and Mortality

Outcomes data are summarized in Table 2. The mortality per site was 29%, 30%, 13%, and 37%, respectively ($p < 0.01$). Transfusions were performed according to institutional practice without sharing of protocols. ENDO patients received the fewest 24-hour RBCs, whereas plasma and platelet transfusions were not different between groups. ENDO patients had the highest 24-hour plasma-RBC ratio. Both median 24-hour plasma-RBC (1.00 vs. 0.14 vs. 0.70 vs. 0.63) and platelet-RBC (0.67 vs. 0.00 vs. 0.28 vs. 0.53) varied significantly between sites (both $p < 0.05$).

Exsanguination was significantly less frequent as a cause of death in ENDO patients (40% vs. 67% vs. 89%), although exsanguination was the most commonly cited cause of death for all groups. TBI and sepsis/multiple organ failure were the second and third most common causes of death in the ENDO group and were more common compared with the OPEN and RT groups. Time to death was significantly longer in ENDO patients (median, 66 vs. 4 vs. 2 hours). Incidence of rebleeding requiring unplanned interventions and ICU-free days between ENDO and OPEN groups were similar. The procedure performed to address rebleeding (OPEN versus ENDO) was not available.

TABLE 1. Demographics and Admission Parameters

Variables	Missing	ENDO (n = 166, 31%)	OPEN (n = 309, 57%)	RT (n = 68, 12%)	*p*
Age, y	0 (0%)	38 (24–52)	31 (23–42)	31 (23–44)	<0.01
Male	0 (0%)	126 (76%)	255 (83%)	56 (82%)	0.20
Blunt	0 (0%)	157 (95%)	104 (34%)	22 (32%)	<0.001
AIS head ≥3	0 (0%)	52 (31%)	38 (12%)	15 (22%)	<0.001
AIS chest ≥3	0 (0%)	116 (70%)	142 (46%)	40 (59%)	<0.001
AIS abdomen ≥3	0 (0%)	127 (77%)	249 (81%)	52 (76%)	0.51
AIS extremity ≥3	0 (0%)	95 (57%)	68 (22%)	29 (29%)	<0.001
ISS	0 (0%)	34 (25–41)	21 (16–30)	27 (24–43)	<0.001
ED SBP, mm Hg	44 (8%)	107 (85–129)	102 (82–125)	91 (74–127)	0.23
ED hypotension*	44 (8%)	48 (30%)	90 (32%)	23 (43%)	0.20
ED GCS	19 (3%)	14 (3–15)	15 (8–15)	8 (3–14)	<0.001
ED base excess, mEq/L	28 (5%)	−7 (−11 to −4)	−7 (−13 to −4)	−16 (−21 to −12)	<0.001
ED shock**	28 (5%)	116 (73%)	213 (71%)	54 (95%)	0.001
ED hemoglobin, g/dL	27 (5%)	11.9 (10.5–13.3)	12.0 (10.4–13.3)	10.9 (9.2–12.6)	<0.01
ED platelet count ($\times 10^9$/L)	43 (8%)	227 (172–289)	216 (155–273)	199 (132–264)	0.06
Time to intervention, min	95 (18%)	298 (200–683)	92 (61–163)	51 (33–89)	<0.001

ED, emergency department; GCS, Glasgow Coma Scale.
*SBP, <90 mm Hg.
**Base excess, < −4 mEq/L.

Description of Vascular Injury

Anatomic locations of bleeding are summarized in Table 3. The overall distribution of NCTH was chest 25%, abdomen 41%, pelvis 31%, and unspecified 3%. Injuries in the ENDO group were most common in the pelvis, whereas injuries in the OPEN and RT groups were most commonly abdominal. In the ENDO group, two anatomic locations of bleeding—the descending thoracic aorta (n = 44, 27%) and the internal iliac arteries (n = 51, 31%)—accounted for over half of all ENDO interventions. Only five (3%) ENDO interventions were for venous bleeding. In contrast, sources of bleeding in the OPEN and RT groups were much more diverse. Many relatively common bleeding sources in the OPEN and RT groups had no representation in the ENDO group.

Multivariable Analysis

Predictive mean matching with age, ISS, AIS scores, mechanism, and treatment were used to impute missing SBP and base excess values for 65 (12%) patients. After imputation, the distribution of SBP and base excess values were unchanged. We constructed a mixed-effects Poisson regression with robust error variance controlling for age, ISS, mechanism, severe head

TABLE 2. Outcomes

Variable	Missing	ENDO (n = 166, 31%)	OPEN (n = 309, 57%)	RT (n = 68, 12%)	*p*
24 h RBC (units)	3 (<1%)	4 (1–11)	8 (3–17)	14 (7–22)	<0.001
24 h Plasma (units)	3 (<1%)	3 (0–10)	4 (0–12)	3 (0–12)	0.38
24 h Plt (units)	3 (<1%)	0 (0–12)	0 (0–6)	1 (0–6)	0.83
24 h Plasma-RBC ratio	3 (<1%)	0.86 (0.25–1.15)	0.67 (0.20–1.00)	0.29 (0–0.69)	<0.001
24 h Plt-RBC ratio	3 (<1%)	0.50 (0–1)	0.14 (0–0.75)	0.08 (0–0.38)	0.20
Rebleeding	3 (<1%)	9 (5%)	9 (3%)	4 (6%)	0.16
ICU-free days	0 (0%)	18 (4–25)	22 (0–27)	0 (0–0)	<0.001
Death	0 (0%)	25 (15%)	63 (20%)	54 (79%)	<0.001
Causes of death*	0 (0%)				
Exsanguination		10 (40%)	42 (67%)	48 (89%)	<0.001
TBI		9 (36%)	6 (10%)	1 (2%)	<0.001
Respiratory		2 (8%)	1 (2%)	2 (4%)	0.34
Sepsis/MOF		8 (32%)	11 (19%)	3 (6%)	0.01
MI/stroke		2 (8%)	3 (5%)	1 (2%)	0.42
Pulmonary embolism		1 (3%)	0 (0%)	0 (0%)	0.18
Time to death, h	0 (0%)	66 (7–185)	4 (2–25)	2 (1–6)	<0.001

*Not mutually exclusive.
RBC, red blood cells; Plt, platelets; MOF, multiple organ failure; MI, myocardial infarction.

TABLE 3. Anatomic Location of Vascular Injury

	ENDO (n = 166, 31%)	OPEN (n = 309, 57%)	RT (n = 68, 12%)
Chest	50 (30.1%)	66 (21.4%)	21 (30.9%)
Pulmonary artery		5 (1.6%)	1 (1.5%)
Ascending aorta	1 (0.6%)	7 (2.3%)	3 (4.4%)
Aortic arch	1 (0.6%)	1 (0.3%)	1 (1.5%)
Innominate artery		2 (0.6%)	
Right subclavian artery	2 (1.2%)	7 (2.3%)	1 (1.5%)
Intrathoracic right common carotid artery		2 (0.6%)	
Intrathoracic left common carotid artery		3 (1%)	
Left subclavian artery	2 (1.2%)	4 (1.3%)	1 (1.5%)
Intercostal/internal thoracic arteries		17 (5.5%)	
Descending thoracic aorta	44 (26.5%)	8 (2.6%)	10 (14.7%)
Pulmonary vein		2 (0.6%)	1 (1.5%)
Superior vena cava		1 (0.3%)	2 (2.9%)
Innominate vein		3 (1%)	
Subclavian vein		4 (1.3%)	1 (1.5%)
Abdomen	37 (22.3%)	154 (49.8%)	34 (50.0%)
Abdominal aorta		6 (1.9%)	4 (5.9%)
Visceral abdominal aorta		1 (0.3%)	1 (1.5%)
Celiac artery		2 (0.6%)	
Common hepatic artery	7 (4.2%)	10 (3.2%)	1 (1.5%)
L hepatic artery	2 (1.2%)	1 (0.3%)	
R hepatic artery	4 (2.4%)	1 (0.3%)	
Splenic artery	6 (3.6%)	4 (1.3%)	1 (1.5%)
Left gastric artery	1 (0.6%)	3 (1%)	
Gastroepiploic artery		3 (1%)	
Superior mesenteric artery		20 (6.5%)	1 (1.5%)
Ileocolic artery		1 (0.3%)	
Inferior mesenteric artery		2 (0.6%)	1 (1.5%)
Other abdominal visceral artery		13 (4.2%)	1 (1.5%)
Renal artery	14 (8.4%)	8 (2.6%)	2 (2.9%)
Infrarenal aorta	1 (0.6%)	4 (1.3%)	1 (1.5%)
Suprarenal/subhepatic inferior vena cava		16 (5.2%)	6 (8.8%)
Retrohepatic inferior vena cava		8 (2.6%)	2 (2.9%)
Portal vein	1 (0.6%)	5 (1.6%)	2 (2.9%)
Splenic vein		9 (2.9%)	1 (1.5%)
Superior mesenteric vein		11 (3.6%)	1 (1.5%)
Renal vein		5 (1.6%)	1 (1.5%)
Gonadal vein	1 (0.6%)	4 (1.3%)	
Infrarenal inferior vena cava		14 (4.5%)	6 (8.8%)
Inferior vena cava, unspecified		3 (1%)	2 (2.9%)
Pelvis	76 (45.8%)	81 (26.2%)	10 (14.7%)
Common iliac artery	1 (0.6%)	7 (2.3%)	3 (4.4%)
External iliac artery	4 (2.4%)	12 (3.9%)	2 (2.9%)
Internal iliac artery	51 (30.7%)	17 (5.5%)	5 (7.4%)
Internal iliac artery branches	17 (10.2%)	13 (4.2%)	
Common iliac vein		18 (5.8%)	
External iliac vein		11 (3.6%)	
Internal iliac vein	3 (1.8%)	3 (1%)	
Unknown	3 (1.8%)	8 (2.6%)	3 (4.4%)

injury (AIS head, ≥3), shock (base excess, ≤4 mEq/L), and hypotension (SBP, <90 mm Hg) as fixed effects and site as a random effect and found that ENDO was associated with reduced in-hospital mortality compared with OPEN (RR, 0.58; 95% confidence interval [CI], 0.46–0.73), whereas RT was associated with increased mortality compared with OPEN (RR, 3.00; 95% CI, 1.84–4.90). We found similar results in a model analyzing only patients with nonmissing SBP and base excess data and

in a model, where OPEN patients, who underwent a concurrent ENDO procedure (n = 9, 3%), were moved to the ENDO group (see Supplemental Digital Content 1, http://links.lww.com/TA/A951).

Because a large proportion of ENDO interventions were performed after blunt thoracic aortic injury (BTAI), possibly for low-grade injuries, we performed a sensitivity analysis using the above covariates and imputed values after excluding patients with BTAI. In this cohort (n = 488), ENDO was associated with reduced mortality compared with OPEN (RR, 0.67; 95% CI, 0.54–0.83).

ENDO Versus OPEN in the Chest Versus Abdomen Versus Pelvis

Exploratory analyses of bleeding for each body cavity (chest, abdomen, or pelvis) were performed (Fig. 1). Using the same covariates as above, use of ENDO was associated with reduced mortality in the chest (n = 137; RR, 0.31; 95% CI, 0.15–0.64) and abdomen (n = 225; RR, 0.38; 95% CI, 0.34–0.44), but not pelvis (n = 167; RR, 1.10; 95% CI, 0.32–3.79).

Diagnostic studies were performed for all multivariable models (see Supplemental Digital Content 1, http://links.lww.com/TA/A951). In terms of global goodness-of-fit, χ^2 tests of the deviance statistic were not significant ($p > 0.05$). Visual inspection of deviance residuals versus predicted values revealed no outliers, and all residuals were within two standard deviations of the mean. Due to the dichotomous outcome, the residuals were not expected to be normally distributed. Instead, we used our model to generate simulated data; visual comparison of actual versus simulated residuals did not reveal large deviations.

DISCUSSION

We performed a retrospective study of adult patients with NCTH presenting to four Level I trauma centers from 2008 to 2012, which collectively represent all of the adult Level I centers in the Houston and San Antonio metropolitan areas. The most common cause of death of all patients in this study was exsanguination (70%): median time to exsanguination was 2 hours (interquartile range, 1 to 5 hours), consistent with other studies of hemorrhaging trauma patients,[4–8] and a testament to the time criticality of hemorrhage control. Using mixed-effects P, we found that ENDO was significantly associated with decreased mortality compared with OPEN in all patients. However, there were significant preintervention disparities between ENDO and OPEN patients. Although ENDO patients had higher ISS, OPEN patients had significantly decreased time to intervention, increased 24-hour RBC transfusions despite shorter time to death, and increased incidence of exsanguination, all consistent with the notion that OPEN patients had substantial on-going hemorrhage at admission, while ENDO patients—although in shock—were stable enough to undergo an ENDO procedure. There were no differences in 24-hour plasma or platelet transfusions, but this may have been due to survivor bias.

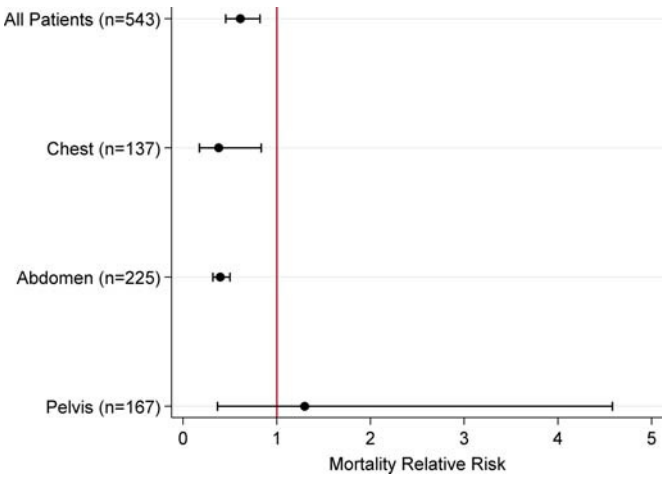

Figure 1. RR of mortality in ENDO versus OPEN groups for all included patients and each anatomic region of bleeding.

Given the ubiquity of ENDO therapy in the elective treatment of vascular disease and its successful use in vascular emergencies, such as ruptured abdominal aortic aneurysm,[19] definitive ENDO treatment of traumatic hemorrhage is becoming increasingly viable.[20] One of the first areas where ENDO treatment was identified as potentially advantageous was bleeding from pelvic fractures.[21,22] Guidelines from the Eastern Association for the Surgery of Trauma (EAST), published in 2011, recommend pursuing ENDO management for any hemodynamically unstable patient with hemorrhage related to pelvic fractures without significant bleeding from another source (Level I recommendation), whereas preperitoneal packing is recommended as salvage therapy after failure of ENDO therapy (Level III recommendation).[23] On the other hand, a more recent guideline from the Western Trauma Association, published in 2016, describes several "complimentary, and not mutually exclusive, options" including pelvic stabilization, preperitoneal packing, REBOA, and ENDO therapy,[24] without clear superiority of any one strategy. A recent multicenter prospective observational study of 1,339 patients with pelvic fracture found that angioembolization and external pelvic fixation were the most common hemorrhage control techniques for arterial and venous bleeding, respectively.[25] Whereas the subgroup with hemorrhagic shock had 32% mortality, a recent single-institution observational study by Burlew et al.[26] found that preperitoneal packing as first-line therapy for 128 patients with hemorrhagic shock from unstable pelvic fractures was associated with mortality of only 21%, challenging the notion that preperitoneal packing should be relegated to salvage therapy. In the present study, mortality in patients with hemorrhagic shock from pelvic hemorrhage was 27%. We found that use of ENDO for pelvic hemorrhage was not associated with improved odds of survival on within-group multiple logistic regression. This was likely because ENDO patients with the most significant hemorrhage were bleeding from the pelvis, consistent with EAST guidelines. Among all 166 ENDO patients, seven (4%) patients exsanguinated within 6 hours of admission, and six of these had bleeding from the pelvis.

In the chest and abdomen, current guidelines recommend that ENDO therapy should be reserved for hemodynamically stable patients, whereas unstable patients should undergo OPEN hemorrhage control.[27–32] Specifically, current data suggest that delayed repair of low-grade (1 or 2) BTAIs is safe, and ENDO therapy is recommended as first-line treatment by 2015 EAST guidelines.[27] Delayed repair of BTAI is justified in the multiple

injuries patient where more immediate lifesaving interventions (e.g., emergent laparotomy or craniotomy) are prioritized, and the aortic injury is temporized by medical blood pressure control before definitive repair.[27] However, patients with high-grade (3 or 4) blunt aortic injuries should not be considered for delayed repair.[28] Current EAST and Western Trauma Association guidelines recommend ENDO intervention for blunt hepatic[29,30] and splenic[31,32] injury only in hemodynamically stable patients. In the present study, ENDO was associated with reduced mortality in the chest and abdomen.

We found that less than 1% of venous injuries were treated by ENDO technique. Disruption of larger and more centrally located veins is required for significant venous hemorrhage due to the lower pressure in the venous system. Patients with injury of large veins often present in profound hemorrhagic shock and are not stable enough to undergo ENDO intervention. At the same time, the ENDO treatment of major venous disruption, such as caval[33] or portal venous injury,[34] is not well described.

One impetus for this study is to generate data to inform the rational development of prehospital NCTH control devices or the prehospital implementation of existing devices (e.g., REBOA). Such devices could save many lives in both the civilian and military sectors in much the same way as the extremity tourniquet,[35] especially if applied early[36] and before the onset of shock.[9–11] However, the danger is that any device which occludes or tamponades blood flow may exacerbate hemorrhage proximal to the occlusion. Therefore, it is essential to establish the anatomic source of NCTH (or at least rule out proximal hemorrhage) if such a device is to be used safely. For example, Hurley and Holcomb[37] performed a retrospective review of 402 patients who underwent emergent laparotomy at a single Level I trauma center, and found that 9% of patients would have benefited from prehospital application of the abdominal aortic junctional tourniquet, because the bleeding source was distal to the aortic bifurcation.

The primary limitation of this study was confounding by indication bias. ENDO interventions were performed almost exclusively for arterial bleeding and for predominantly few anatomic locations. As a whole, ENDO patients had significantly longer times to intervention, longer times to death, and decreased incidence of exsanguination—all suggesting that ENDO patients were generally hemodynamically stable enough for an ENDO procedure, whereas OPEN patients more often had substantial ongoing hemorrhage at time of admission. Exceptions included patients with substantial pelvic hemorrhage who underwent ENDO. Indicators of response to initial resuscitation—such as number of blood products transfused within the first few hours after admission, presence of computed tomography scan before definitive hemorrhage control, and perioperative vital signs or laboratory data—could have been used to stratify patients by degree of ongoing hemorrhage, but were unfortunately not available for this retrospective study. The ENDO group likely included patients with low-grade injury who were at low risk for hemorrhage, but we lacked data regarding the grade of blunt arterial injury to exclude these patients. Another limitation is that only one patient underwent REBOA during this period. The use of REBOA is increasing, is safe in high volume-centers,[38] and is at least as effective as RT in achieving aortic occlusion without the morbidity of a highly invasive procedure.[39] It is unclear what impact REBOA has in the decision making of ENDO versus OPEN control of NCTH, and this should be investigated in future studies. It is also unknown how many OPEN patients underwent exploration primarily for identification and repair of nonvascular injuries (e.g., bowel injuries) with incidental intraoperative control of hemorrhage. However, there were likely few such patients, given that OPEN patients had evidence of increased on-going hemorrhage as described above. Additionally, we observed a strong association between ENDO and decreased mortality, whereas a significant number of OPEN patients who were at low risk for exsanguination would have diluted this association. Although we sought to identify all adult patients with significant NCTH who survived to hospital presentation, this study does not include those successfully managed at a non–Level I facility, or those who presented to a non–Level I facility and died before transfer. Comprehensive autopsy studies will be required to definitively address the magnitude of this problem.

In conclusion, use of ENDO techniques for nonelective indications is increasing. In this study of patients with NCTH, ENDO treatment was used predominantly after blunt mechanism, in a much more delayed fashion, and for a narrower range of anatomic injuries compared to OPEN hemorrhage control. Its use seems consistent with current guidelines. Although ENDO treatment in this study was significantly associated with decreased mortality in all patients, significant between-group differences limit the generalizability of this finding.

AUTHORSHIP

E.E.F., B.J.E., R.G., K.K.C., J.M.P., C.E.W., and J.B.H. participated in the study inception and design. E.E.F., B.J.E., R.G., K.K.C., S.M.D., J.J.D., J.S.T., G.R.F., V.G.S., S.R.T., and J.M.P. participated in data acquisition. R.C., E.E.F., T.J.G., and S.M.D participated in data analysis. All authors contributed to the article preparation.

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DISCLOSURE

Conflict of Interest: J.B.H is the co-inventor of the Junctional Emergency Treatment Tool (JETT). All other authors report no conflicts of interest.
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EDITORIAL CRITIQUE

Dr. Chang and his team are to be congratulated for a comprehensive review of over 500 patients treated at multiple urban level I trauma centers over 4 years, aimed at precisely describing the specific anatomic locations of non-compressible torso hemorrhage (NCTH) and characterizing the features of the endovascular (ENDO) vs open (OPEN) approach to addressing said injuries. As with any clinical problem, understanding exactly what we are dealing with is the first step to innovating new solutions and refining current ones.

The authors report a decreased mortality in patients with NCTH undergoing ENDO vs OPEN approaches to hemorrhage control. The main limitation related to the reported decrease in mortality in the ENDO group, as recognized in the article, are the significant differences between the groups being compared. The two groups are arguably not clinically comparable groups obviating the utility of a statistical comparison.

However, the present article is an excellent and detailed description of a wide range of injuries resulting in NCTH and their management. Among several interesting observations, the authors noted a significant increase in the use of ENDO to control hemorrhage over the 4-year timeframe of the study (from 21% up to 41%). Advances in technology such as the hybrid operating room and devices for NCTH control, being developed and employed as early as the pre-hospital setting, (examples that the authors note) are sure to push the use of ENDO even higher in years to come.

The patients included in the present study were managed consistent with current practice recommendations, including the EAST guidelines, advocating for endovascular techniques depending on anatomic location of hemorrhage and patient physiology. Practice guidelines will undoubtedly evolve and be revised, with broadening criteria for injury severity and clinical stability acceptable for endovascular management as the aforementioned technology is refined and studied. I look forward to following the author team's continued work in the field, confident it will be instrumental in the ongoing changes we will see in the care of injured patients who sustain NCTH.

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U C Davis Medical Center
Sacramento, California

TOO FAST, OR NOT FAST ENOUGH? THE FAST EXAM IN PATIENTS WITH NON-COMPRESSIBLE TORSO HEMORRHAGE

Woo S. Do, MD; Matthew J. Eckert, MD; Erin Fox, PhD; John B. Holcomb, MD; Matthew J. Martin, MD and the NCTH Study Group

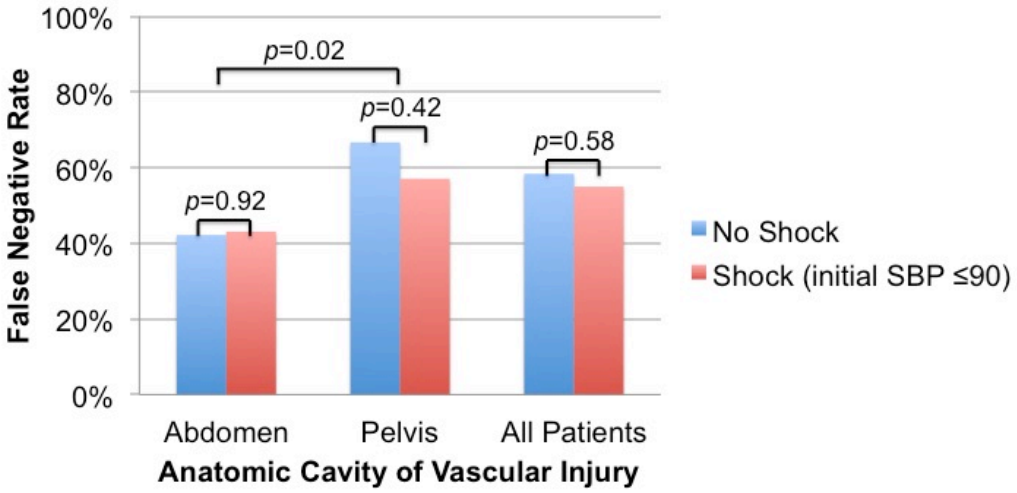
OBJECTIVES: Trauma surgeons assessing patients with non-compressible torso hemorrhage (NCTH) often rely on the focused assessment with sonography for trauma (FAST) as an initial point of care imaging study. The objective of this study was to describe the metrics of FAST as a stand-alone study in a large cohort with NCTH.

METHODS: Retrospective review of a dedicated NCTH database from four level 1 trauma centers (2008-2012). NCTH was defined as (1) named axial torso vessel disruption; (2) abbreviated injury scale (AIS) chest or abdomen ≥3 with shock (base deficit <-4) or truncal operation in ≤90 minutes; or (3) pelvic fracture with ring disruption. Patients were grouped by anatomic location of primary source of hemorrhage (abdomen vs. pelvis) and by hemodynamic instability (SBP ≤90).

RESULTS: 274 patients had a FAST exam prior to diagnosis of NCTH (50% by operative exploration, 28% by CTA, 19% by angiography). The source of NCTH was the chest in 84 patients, abdominal in 119, and pelvic in 71. Demographics including age, mechanism, SBP, and ISS were not different between abdominal vs pelvic NCTH (all p=NS). The FAST was positive in only 51% of patients with abdominal or pelvic hemorrhage for an overall false negative rate of 49%. The false negative rate was significantly higher for pelvic (61%) versus abdominal (43%) sources (p=0.02). There was no difference between FAST negative or positive patients for ISS, shock, length of stay, or mortality (all p=NS). FAST performance metrics were not improved among the subgroup of NCTH patients with hemodynamic instability at presentation (Figure).

CONCLUSION: The initial FAST exam identified abdominal or pelvic hemorrhage in approximately half of NCTH patients, and this was not significantly improved among NCTH patients presenting with hemodynamic instability or shock. The high false negative rate, particularly for pelvic sources, must be considered when interpreting and acting on this screening study.

Figure 1. FAST Exam False Negative Rate by Location of Vascular Injury



Appendix 3. Regulatory documents for the prospective study from Y3Q4

DEPARTMENT OF THE ARMY
HEADQUARTERS, US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
810 SCHREIDER STREET
FORT DETRICK, MD 21702-5000

REPLY TO
ATTENTION OF

MCMR-RPI

29 June 2017

MEMORANDUM FOR RECORD

SUBJECT: Initial Approval of the Protocol, "Hemorrhage Control for Major Traumatic Vascular Injuries: Phase II: A Prospective Observational Study of Non-Compressible Torso Hemorrhage (NCTH)," Submitted in Support of Proposal, "Hemorrhage Control for Major Traumatic Vascular Injuries," Proposal Principal Investigator: John B. Holcomb, MD, University of Texas Health Science Center, Houston, TX, Proposal No. 13057176, Award No. W81XWH-14-1-0112, Site Principal Investigator: LTC Jennifer Gurney, US Army Institute of Surgical Research (USAISR), Joint Base San Antonio, TX, USAISR Protocol Number IRB H-16-037, HRPO Log No. A-18067.2e, IRB Protocol Number M-10663

1. The Headquarters, US Army Medical Research and Materiel Command Institutional Review Board (HQ USAMRMC IRB) reviewed the above-referenced research protocol for compliance with applicable human subject protection regulations. There are no outstanding human research protections issues.

2. In accordance with 32 CFR 219.110(a,b), the research qualifies for review via an expedited review procedure as it involves no more than minimal risk and is included in the categories of research listed in the 9 November 1998 Notice in the Federal Register (63 FR 60364-60367), specifically, research involving materials that have been, or will be collected solely for nonresearch purposes (Category 5).

3. The research protocol is approved for a one-year period, 29 June 2017- 28 June 2018, pending any required approvals at the USAISR.

4. The study is approved to enroll patients admitted to the emergency department through November 2017 with a known or suspected non-compressible hemorrhage who meet study eligibility criteria.

5. The requirement to obtain informed consent is waived as allowed under 32 CFR 219.116(d) as the research involves no more than minimal risk to the subjects, the waiver will not adversely affect the rights and welfare of the subjects, and the research could not practicably be carried without the waiver.

6. A waiver of the Health Insurance Portability and Accountability Act Privacy Rule requirement to obtain authorization for the use and disclosure of protected health information in research is approved as allowed under DOD 6025.18-R, C7.9.2.2.

7. Approved documents: Sponsor Protocol (Version 2.0, dated 04JAN2017) and Site-specific Protocol (Version 1, dated 23 May 2017).

MCMR-RPI
SUBJECT: Initial Approval of the Protocol, "Hemorrhage Control for Major Traumatic Vascular Injuries: Phase II: A Prospective Observational Study of Non-Compressible Torso Hemorrhage (NCTH)," Submitted in Support of Proposal, "Hemorrhage Control for Major Traumatic Vascular Injuries," Proposal Principal Investigator: John B. Holcomb, MD, University of Texas Health Science Center, Houston, TX, Proposal No. 13057176, Award No. W81XWH-14-1-0112, Site Principal Investigator: LTC Jennifer Gurney, US Army Institute of Surgical Research (USAISR), Joint Base San Antonio, TX, USAISR Protocol Number IRB H-16-037, HRPO Log No. A-18067.2e, IRB Protocol Number M-10663

8. Please note the following requirements:

a. Submit all proposed changes to the study for review and approval by the HQ USAMRMC IRB before initiating the changes.

b. Promptly report to the HQ USAMRMC IRB:

(1) All unanticipated problems involving risks to subjects or others [,unanticipated adverse device effects,] and related serious adverse events.

(2) Any protocol deviation that affects subjects' safety or rights and/or the integrity of the study.

c. Submit a continuation report, a copy of the current protocol and supporting documents to the HQ USAMRMC IRB at least 30 days prior to IRB approval expiration to ensure timely review and approval.

d. Submit a final study report and request to close the protocol upon completion of all research activities.

9. The Office of Research Protections IRB Office point of contact for this action is Debra DePaul, RN, MSN, General Dynamics Health Solutions, at 301-619-2620 or debra.depaul.ctr@mail.mil.

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Date: 2017.06.29 16:47:34 -04'00'

LAURA R. BROSCH, RN, PhD
Designated Expedited Review IRB Member
Headquarters, US Army Medical Research and Materiel Command
Institutional Review Board

Appendix 4. Quad Chart

Hemorrhage Control for Major Traumatic Vascular Injuries

EDMS: 5840 and Quad Chart for Year 3 Annual Report
W81XWH-14-1-0112

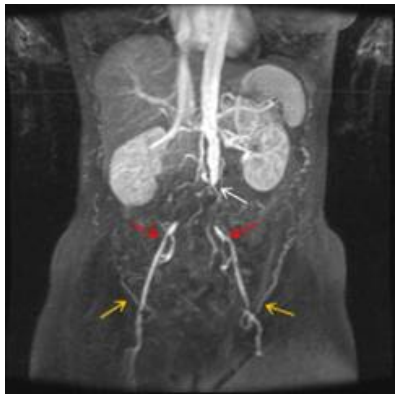
PI: John B. Holcomb, MD/ Laura J. Moore, MD **Org:** University of Texas Health Science Center at Houston **Award Amount:** $1,991,317

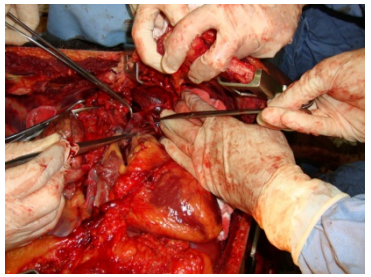
Study Aims

- Determine current practice patterns for the treatment of patients with non-compressible torso hemorrhage (NCTH) among 4 clinical sites using a retrospective study design;
- Conduct a 2-day Delphi Panel meeting of military and civilian experts to gain consensus regarding anatomic, technology, credentialing, competency, and training issues for catheter-based hemorrhage control and inform the development of the prospective study.
- Conduct a 4-site prospective observational study to test the hypo-thesis that less-invasive device-driven and expert-let hemorrhage control techniques improve survival in NCTH patients and definitively inform development of catheters, devices and training required for catheter-based hemorrhage control.

Approach

This is a 2-phase study which will include a retrospective study and Delphi Meeting in Phase I, then a prospective study in Phase II informed by the Phase I activities.





These pictures represent the care of the severely injured NCTH patient, which will be studied in this project.

Accomplishments this quarter: Phase I- Manuscript published and abstract submitted. Phase II- Continued patient enrollment in prospective study at 4 sites with 228 patients enrolled to date. All regulatory approvals are current.

Timeline and Cost

Activities	Y1	Y2	Y3	Y4
Phase 1 milestones	→	→		
Obtain IRB approvals for prospective study		→	→	
Conduct prospective study			→	→
Data analysis/ publication				→
Estimated Budget ($K)	**994**	**996**	**EWOF 1**	**EWOF 2**

Updated: September 14, 2017

Goals/Milestones

CY14 -15 Goals – Phase I

- ❑ Obtain DoD HPRO and local IRB approvals
- ❑ Conduct retrospective data collection
- ❑ Analysis of retrospective data
- ❑ Hold Delphi Panel meeting

CY15-16 and EWOF Goals – Phase II

- ❑ Obtain regulatory approvals for prospective study
- ❑ Conduct prospective observational study
- ❑ Data Analysis/Publications

Comments/Challenges/Issues/Concerns

- The prospective study will be completed in an EWOF Year 4 as well as data analysis and manuscript development. There are no other financial or scientific concerns. The 2nd EWOF has been requested.
- **Budget Expenditure to Date**

Projected Expenditure: Y3Q4 $0K; YTD $0K; ITD $1,991K
Estimated Actual Expenditure: Y3Q4 $157K; YTD $888K; ITD $1,694K